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Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196
www.cc.nih.gov/phar

Robert DeChristoforo, M.S.
Acting Chief, Pharmacy Department

Editor
Karim Anton Calis, Pharm.D., M.P.H.
Clinical Specialist, Endocrinology & Women's Health, and Coordinator, Drug Information Service
kcalis@nih.gov

In This Issue

Drug-Induced Glucose and Insulin Dysregulation

Glucose homeostasis is regulated by the complex interplay of insulin, hepatic glucose production, peripheral glucose utilization, and counterregulatory mechanisms. Insulin is secreted by pancreatic beta-cells in response to an increase in plasma glucose. It promotes glucose uptake by the liver, muscle, and adipose tissue. Insulin stimulates glycogen synthesis, lipogenesis, and protein synthesis and inhibits lipolysis and hepatic gluconeogenesis. In healthy individuals, a normal plasma glucose level is needed to maintain physiological functions and meet the energy needs of the brain and various tissues. Insulin secretion decreases as plasma glucose level falls. When plasma glucose concentrations decrease below the physiological range, counterregulatory hormones are secreted. These include glucagon, adrenaline (epinephrine), growth hormone, and cortisol. These hormones have various effects on restoring plasma glucose to the physiologic range, including stimulating gluconeogenesis and glycogenolysis, inhibiting insulin secretion, inhibiting peripheral glucose utilization, and stimulating lipolysis. Hypoglycemia and hyperglycemia both result from an imbalance between plasma glucose and insulin levels. Drugs may induce hyper- or hypoglycemia through a variety of mechanisms, including alterations of insulin secretion and sensitivity, changes in gluconeogenesis, and direct cytotoxic effects on pancreatic beta-cells. Drug-induced hyper- or hypoglycemia can lead to significant consequences, including diabetes mellitus, severe hypoglycemia, coma, and death. However, these events can be prevented and/or minimized with awareness of the problem, close monitoring, and judicious use of the suspect drug(s).

Causative Agents

Tables 1 and 2 list the medications and incidence that have been associated with alterations in glucose and/or insulin regulation. While there are reports of many other drugs in the literature, only drugs with adequate data to establish a clear relationship between its administration and drug-induced hyperglycemia or hypoglycemia will be discussed in this chapter. Glucocorticoids, protease inhibitors, atypical antipsychotics, niacin, pentamidine, and diazoxide are the agents that have most consistently induced hyperglycemia and diabetes mellitus. For hypoglycemia, the most important causative agents are insulin, sulfonylureas, and ethanol, either used alone or in combination. These agents account for over 70 percent of cases of severe hypoglycemia in a review of 1,418 cases reported between 1940 and 1989.[1] In children 2 years of age or younger, salicylate poisoning causes the majority of drug-induced hypoglycemia.[1]

Epidemiology

The true incidence of glucose and insulin dysregulation associated with most drugs is unknown due a variety of factors, including lack of data from controlled clinical trials, underreporting of postmarketing adverse drug reactions, and the fact that not all cases have been definitively proven to be drug related. For some drugs, the rate of drug-induced hyperglycemia or hypoglycemia may also vary depending on the dose, frequency, and/or duration of drug administration as well as the underlying disease state of the patient. For example, in the Diabetes Control and Complications Trial, the incidence of severe hypoglycemia from insulin administration was threefold higher in the intensively treated (insulin

Table 1. Agents That May Induce Hyperglycemia and Diabetes Mellitus

Drug or Drug Class	Mechanism(s)	Incidence*	Clinical Significance†	References
Atypical antipsychotics	↓ peripheral insulin sensitivity, ↓ insulin secretion, promote weight gain (all proposed)	NK; highest incidence with olanzapine and clozapine.	++	3, 4, 14, 23-29
Beta-adrenergic receptor blockers	↓ insulin secretion, ↓ insulin sensitivity; effects attenuated but not abolished with cardioselective beta blockers.	NK; incidence higher with nonselective beta blockers.	++	30-32
Calcium channel antagonists	↓ insulin secretion	rare	+	33-35
Cyclosporine	↓ insulin production, inhibits insulin secretion, ↓ beta-cell volume and function, ↑ insulin resistance	New-onset PTDM: 4-11% in kidney transplant patients	++	36-40
Diazoxide	↓ insulin secretion, may also ↑ glucose production and ↑ glucose uptake	NK	+++	41-44
Didanosine	Causes pancreatitis leading to beta-cell injury. Inhibits insulin release secondary to hypokalemia (proposed). See also nucleoside reverse transcriptase inhibitors.	NK	++	37, 45, 46
Diuretics	↓ insulin release secondary to hypokalemia, ↓ insulin sensitivity	NK; most commonly reported with thiazides. Incidence is lower with doses less than 25 mg of HCTZ equivalent.	++	9, 47-49
Fish oil	Unknown	NK. Usually only occurs in patients with impaired glucose tolerance or diabetes mellitus. Risk is usually associated with doses >3 g/day. Some data also show no significant changes in glycemic control in diabetic patients.	+	50-54
Gatifloxacin	Unknown	NK	++	55-60
Glucocorticoids	↑ gluconeogenesis, ↑ insulin resistance, ↓ pancreatic insulin secretion	Less than 1-46% for new-onset diabetes. Incidence varies depending on dose, duration, and route of administration. Lower incidence with inhaled formulations.	+++	7, 9, 61-67
Growth hormone	causes insulin resistance	NK	+	37, 68, 69
Interferons	formation of islet cell antibodies	NK	+	70, 71
l-asparaginase	↓ insulin synthesis	NK	++	37, 72-74
Megesterol acetate	↓ insulin sensitivity and promotes weight gain (proposed). Binds to glucocorticoid receptor.	NK	++	37, 75-81
Niacin (nicotinic acid)	↓ insulin sensitivity, ↑ hepatic gluconeogenesis	NK	++	37, 82-84
Nucleoside reverse transcriptase inhibitors (excluding didanosine)	↑ insulin resistance, promote lipodystrophy. Can also cause pancreatitis.	NK	+	85-87
Oral contraceptives	↓ peripheral insulin sensitivity	NK. More common with formulations containing high-dose estrogen (> 35 mcg ethinyl estradiol or equivalent) or 2nd-generation progestin.	+	88-92
Pentamidine	Direct cytolytic effects on pancreatic beta cells; causes hypoglycemia initially. Effect may be irreversible. Can also cause pancreatitis.	NK	+++	93-100
Phenothiazines	↓ insulin secretion, promote weight gain, may cause insulin aggregation and inactivation	NK, most case reports are of chlorpromazine.	+	101, 102
Phenytoin	↓ insulin secretion, may also ↓ insulin sensitivity	Rare	+	103-106
Protease inhibitors	↓ insulin resistance directly or indirectly, promote lipodystrophy, ↓ insulin secretion (proposed)	5% for new-onset diabetes mellitus; up to 40% for impaired glucose tolerance	++	22, 107-114
Rifampin	Unknown, may ↑ intestinal absorption of glucose	NK	+	115
Ritodrine	↑ hepatic gluconeogenesis (proposed)	NK	++	116-118
Tacrolimus	↓ insulin secretion, ↓ insulin sensitivity. May cause pancreatic islet cell toxicity. Hyperglycemia and diabetes mellitus reported without use of concomitant corticosteroids.	New-onset insulin-dependent PTDM: 20% (kidney transplant patients), 11-18% (liver transplant patients). Hyperglycemia: 22% (kidney transplant patients), 33-47% (liver transplant patients). Patients received concomitant steroid therapy. Lower incidence 1 year post transplant. Higher incidence with tacrolimus than with cyclosporine.	++	36, 40, 119-122
Terbutaline	↑ gluconeogenesis & glycogenolysis, ↓ peripheral insulin sensitivity	NK	++	123-125
Thalidomide	↓ insulin-stimulated glucose uptake and glycogen synthesis	NK	+	126, 127

Abbreviations:

↑ = increases, ↓ = decreases, NK = not known, HCTZ = hydrochlorothiazide, PTDM = post-transplant diabetes mellitus

* Incidence may be related to drug dose.

† Clinical significance based on authors' consensus as to the strength of evidence, magnitude of effect, and frequency.

Table 2. Agents That May Induce Hypoglycemia

Drug or Drug Class	Mechanism(s)	Incidence*	Clinical Significance†	References
Angiotensin-converting enzyme inhibitors	↑ peripheral insulin sensitivity (proposed)	NK	+	17, 128-130
Beta-adrenergic receptor blockers	Mask many autonomic hypoglycemic symptoms, can delay recovery from hypoglycemia. May ↑ peripheral glucose uptake and indirectly ↓ gluconeogenesis.	NK; effects more commonly associated with nonselective beta blockers.	++	1, 30, 131-133
Bitter melon (*Momordica charantia*) (also commonly known as karela)	Proposed: components of extracts structurally similar to animal insulin, ↑ insulin secretion, ↑ tissue glucose uptake, ↑ hepatic glycogen synthesis, ↑ peripheral glucose oxidation in erythrocytes and adipocytes, ↓ hepatic gluconeogenesis	NK	+	134-139
Cinnamon	↑ insulin sensitivity (proposed)	NK	+	140
Disopyramide	↑ insulin secretion	NK	++	141-145
Ethanol	Inhibits hepatic gluconeogenesis, impairs activation of the HPA axis's hormonal response to hypoglycemia, can potentiate hypoglycemic effects of other drugs. More problematic when glycogen stores are low.	NK	+++	1, 17, 131
Fenugreek (*Trigonella foenum graecum*)	Proposed: slows carbohydrate absorption, inhibits glucose transport	NK	+	139, 146, 147
Fluoroquinolones	Unknown, may be due to stimulation of pancreatic insulin secretion and/or interaction with antidiabetics. Most reports with gatifloxacin. Resistant hypoglycemia (resolves with discontinuation only) may occur.	NK	++	55, 56, 148-153
Ginseng	Proposed: ↓ rate of carbohydrate absorption into portal hepatic circulation, ↑ glucose transport and uptake mediated by nitric oxide, ↑ glycogen storage, modulation of insulin secretion. Most clinical trials done using American ginseng (*Panax quiquefolius*).	NK	+	139, 154-157
Insulin	↑ glucose utilization	Varies: 2.76-62 episodes per 100 patient-years for severe hypoglycemia requiring assistance. Higher incidence in type 1 versus type 2 diabetics.	+++	2, 18, 158
Ivy gourd (*Coccinia indica)*	insulin-mimetic (proposed)	NK	+	139, 159
L-carnitine	Proposed: ↑ insulin sensitivity, ↑ glucose uptake and storage	NK	+	139, 160-162
Meglitinides (nonsulfonylurea secretagogues)	↑ pancreatic insulin secretion	NK; lower incidence compared to sulfonylureas.	+++	163-165
Pentamidine	↑ insulin release through direct cytotoxic effects to pancreatic beta cells (see table 1)	6-40% with intravenous or intramuscular formulations, 1% or less with nebulized formulation.	+++	8, 93, 97, 99, 166-168
Quinine	↑ pancreatic insulin secretion, usually high doses or rapid IV infusion needed. *Plasmodium falciparum* infection itself is associated with hypoglycemia.	NK	++	131, 169-173
Quinidine	↑ pancreatic insulin secretion. See quinine.	NK	++	131, 174
Salicylates	Proposed: ↑ pancreatic insulin secretion, ↑ peripheral glucose utilization, ↓ gluconeogenesis. Usually occurs only with anti-inflammatory doses.	NK	+ in adults, +++ in children. Most common cause of severe hypoglycemia in children ≤ 2 years.	1, 131, 175
Sulfonamide antibiotics	↑ pancreatic insulin secretion (proposed)	NK; rare reaction with renal failure and/or high doses.	+	176-179
Sulfonylureas	↑ pancreatic insulin secretion	Varies: 1.8% per year for recorded hypoglycemia, 1.23 per 100 person-years or 3.3% for severe hypoglycemia. Higher incidence reported with chlorpropamide and glyburide.	+++	1, 5, 6, 158, 180

Abbreviations:

↑ = increases, ↓ = decreases, NK = not known, HPA = hypothalamic-pituitary-adrenal.

* Incidence may be related to drug dose.

† Clinical significance based on authors' consensus as to the strength of evidence, magnitude of effect, and frequency.

pump or ≥ 3 daily insulin injections) diabetes group compared to the conventionally treated (1-2 daily insulin injections) group.[2] Within a specific drug class, the incidence of drug-induced hyper- or hypoglycemia may also vary. For example, hyperglycemia and diabetes mellitus is more commonly seen with olanzapine and clozapine compared to the other atypical antipsychotic drugs.[3,4] The incidence of hyperglycemia may also be higher if the patient has predisposing risk factors for diabetes mellitus (see Table 3). Hypoglycemia is more common with long-acting (e.g., chlorpropamide and glyburide) than shorter-acting sulfonylureas (e.g., tolbutamide).[5,6] The reported incidence of drug-induced hypoglycemia may also vary depending on how hypoglycemia was defined. Additionally, factors such as the presence of active metabolites, the route of elimination, and whether the patient has other risk factors (see Table 4) for hypoglycemia also account for the difference in incidence of hypoglycemia among the drugs. Finally, the route of administration, and therefore the systemic availability of a drug, may also influence the incidence of the drug-induced condition. For example, corticosteroids and pentamidine administered by the inhalation route infrequently cause alterations in glucose homeostasis, unlike their injectable or orally administered dosage forms.[7,8]

Table 3. Risk Factors for Drug-induced Hyperglycemia and Diabetes Mellitus

Patients with underlying risk factors for type 2 diabetes mellitus[10]

- ❖ age ≥ 45 years
- ❖ overweight (BMI ≥ 25 kg/m^2)
- ❖ family history of diabetes
- ❖ habitual physical inactivity
- ❖ race/ethnicity (e.g., African Americans, Hispanic Americans, Native Americans, Asian Americans, and Pacific Islanders)
- ❖ previously identified impaired fasting glucose or impaired glucose tolerance
- ❖ history of gestational diabetes mellitus or delivery of a baby weighing > 9 lbs
- ❖ hypertension (≥ 140/90 mmHg in adults)
- ❖ high density lipoprotein cholesterol ≤ 35 mg/dl (0.90 mmol/l) and/or a triglyceride level ≥ 250 mg/dl (2.82 mmol/l)
- ❖ polycystic ovary syndrome
- ❖ history of vascular disease

Dose of suspect drug*

Use of more than one drug that can induce hyperglycemia

Drug interactions – use of drugs that may increase the concentration and/or hyperglycemic effect of offending drug

* Some drugs exhibit a dose-related effect on hyperglycemia (e.g., corticosteroids, hydrochlorothiazide). However, the dose-related hyperglycemic effects of most drugs are unknown.

Table 4. Risk Factors for Drug-induced Hypoglycemia

Advanced age

Renal dysfunction

Hepatic dysfunction

Dose of offending drug

Decreased carbohydrate intake

Reduced carbohydrate stores

Use of more than one drug that can induce hypoglycemia

Drug interactions – use of drugs that may increase the concentration and/or hypoglycemic effect of suspect drug

Hospitalization within past 30 days

Recent alcohol use

Mechanisms

Drugs induce hyper- or hypoglycemia through a variety of mechanisms, including alterations of insulin secretion, changes in insulin sensitivity (either directly at the receptor level or by indirectly promoting weight gain or changes in adipose tissue), changes in gluconeogenesis or glucose metabolism, and direct cytotoxic effects on pancreatic beta-cells. Tables 1 and 2 list the known or proposed mechanisms by which specific agents may cause alterations in glucose or insulin regulation. For some drugs, it is not clear whether the diabetes mellitus is a direct drug effect or if the drug is merely a contributing factor, unmasking preexisting diabetes in individuals already at risk for the disease.[9] Drugs may also induce hyper- or hypoglycemia by causing pancreatitis. Drug-induced pancreatitis is discussed in chapter 38.

Clinical Presentation and Differential Diagnosis

The signs and symptoms of hyperglycemia and diabetes mellitus are listed in Table 5. The diagnosis of diabetes mellitus can be made if any of the following three criteria are met: fasting plasma glucose ≥ 126 mg/dl on two separate occasions, symptoms of diabetes and random plasma glucose ≥ 200 mg/dl, or plasma glucose ≥ 200 mg/dl two hours after a 75 gram oral glucose load.[10] Depending on the drug, hyperglycemia can appear within hours or several weeks to months after administration of the offending agent. Severe hyperglycemia manifesting as diabetic ketoacidosis and hyperglycemic coma may be seen.

Table 6 lists the typical signs and symptoms associated with hypoglycemia although there is considerable inter-individual variation. The glycemic threshold at which patients experience hypoglycemic symptoms varies. Typically, symptoms begin to manifest at a plasma glucose of approximately 55 mg/dl. However, factors such as prolonged hyperglycemia, caffeine use, or frequent episodes of hypoglycemia may shift this threshold up or down. Most patients develop hypoglycemia unawareness if they experience

repeated episodes of hypoglycemia over a short period of time. Patients with hypoglycemia unawareness do not experience typical hypoglycemic symptoms and may fail to take corrective actions due to central nervous system impairment.[11] Severe hypoglycemia can lead to cognitive dysfunction, mental status changes, seizures, coma, and death. Therefore, close monitoring and patient education should be instituted when a drug with the potential for hypoglycemia is initiated.

Before the diagnosis of drug-induced hyperglycemia or hypoglycemia can be made, other possible causes of hyper- or hypoglycemia must be ruled out (Table 7). Hyperglycemia may occur during periods of physiologic stress such as surgery, fever, or trauma. Hyperglycemia associated with Cushing's syndrome may be the result of either exogenous administration or endogenous overproduction of glucocorticoids. When assessing possible causes of hypoglycemia, intentional self-administration of hypoglycemic drugs (usually insulin or a sulfonylurea), intentional overdose by a patient with diabetes (i.e., factitious or iatrogenic hypoglycemia),[12] and medication-dispensing errors must always be considered. Hypoglycemia is also frequently seen in acutely ill patients. Uncommon causes of hypoglycemia include insulin-producing tumors (i.e., an insulinoma) and several other rare disorders (Table 7).[13] Drug-induced hyper- or hypoglycemia may be differentiated from other possible etiologies by evaluating the temporal relationship between drug administration and onset of the symptoms and blood glucose changes. Drug withdrawal and rechallenge may be helpful to confirm the diagnosis.

Table 5. Signs and Symptoms Associated with Hyperglycemia and Diabetes Mellitus

Mild to moderate

- Excessive thirst and polydipsia
- Polyuria
- Blurry vision
- Polyphagia
- Unexplained weight loss
- Increased fatigue

Severe

- Nausea and vomiting
- Lethargy
- Obtundation
- Abdominal pain
- Breath with fruity odor
- Dehydration
- Metabolic acidosis
- Coma

Table 6. Signs and Symptoms Associated with Hypoglycemia

Mild to moderate

- Hunger
- Sweating/diaphoresis
- Tachycardia
- Shakiness/tremors
- Dizziness
- Headache
- Weakness

Severe

- Blurry vision
- Confusion and difficulty concentrating
- Behavioral changes such as anxiety and irritability
- Seizure
- Loss of consciousness
- Coma

Table 7. Differential Diagnoses for Drug-induced Glucose and Insulin Dysregulation

Hyperglycemia and diabetes mellitus

- Cushing's syndrome
- Liver cirrhosis
- Metabolic acidosis
- Pancreatitis
- Parenteral nutrition therapy (dextrose administration)
- Renal failure
- Stress hyperglycemia

Hypoglycemia*

- Acquired severe liver disease
- Addison's disease
- Beckwith-Wiedemann syndrome
- Carnitine deficiency
- Congestive heart failure
- Defective type 1 glucose transporter in the brain
- Erythroblastosis fetalis
- Factitious or iatrogenic hypoglycemia
- Galactosemia
- Glycogen storage disease
- Hereditary fructose intolerance
- Hypopituitarism
- Insulinoma
- Islet cell hyperplasia/nesidioblastosis
- Isolated growth hormone deficiency
- Isolated adrenocorticotropic hormone deficiency
- Lactic acidosis
- Large non-beta cell tumor
- Noninsulinoma pancreatogenous hypoglycemia syndrome
- Persistent hyperinsulinemic hypoglycemia of infancy
- Postoperative removal of pheochromocytoma
- Renal failure
- Reye's syndrome
- Sepsis
- Small size for gestational age infants

* Adapted from reference 13.

Risk Factors

Tables 3 and 4 lists the risk factors for drug-induced hyperglycemia and hypoglycemia. Patients with predisposing factors for type 2 diabetes mellitus are particularly at risk for drug-induced hyperglycemia since some drugs can worsen preexisting insulin resistance and beta cell dysfunction. Some drugs may also unmask preexisting diabetes mellitus. The patient's underlying disease state(s) can play an important role in the risk of developing hyper- or hypoglycemia. For example, hypertension and schizophrenia are associated with a higher incidence of diabetes mellitus and may also contribute to or confound the diagnosis of drug-induced hyperglycemia.[10, 14] Polypharmacy is an important risk factor since the use of more than one drug that can induce glucose or insulin dysregulation can lead to additive effects through pharmacodynamic and pharmacokinetic drug interactions. For example, the combined use of sulfonylureas and some non-steroidal anti-inflammatory agents may lead to an increased risk of hypoglycemia due to increased sulfonylurea serum concentrations.[15]

Morbidity and Mortality

Hyperglycemia induced by drugs may be transient or may result in permanent changes in glucose regulation. Similar to other causes of diabetes mellitus, drug-induced hyperglycemia is believed to increase the risk of microvascular complications (retinopathy, neuropathy, nephropathy), macrovascular complications (atherosclerotic cardiovascular disease, cerebrovascular disease, and peripheral vascular disease), delayed healing of infections, hyperosmolar coma, and death. Cases of diabetic ketoacidosis and death have been reported with many of the agents listed in Table 1. Diabetic nephropathy, sensorimotor peripheral neuropathy, ketoacidosis, hyperosmolar coma or precoma, myocardial infarction, and stroke were reported in a cohort study of renal transplant patients who developed post-transplant diabetes mellitus and followed for a mean of 9.3±1.5 years. The immunosuppressive regimen in these patients consisted of cyclosporine and corticosteroids.[16] Drug-induced hypoglycemia often produces only transient and mild-to-moderate symptoms. However, patients may experience inconvenience, reduced quality of life, or discontinue treatment due to fear of future hypoglycemic episodes. Severe hypoglycemia can lead to mental status changes, seizure, loss of consciousness, permanent neurological damage, and death. Severe hypoglycemia from sulfonylureas results in permanent neurological deficits in 5 percent of survivors and has a reported mortality rate of 10 percent. Insulin-induced hypoglycemia causes approximately 2 to 4 percent of deaths in patients with type 1 diabetes.[17,18] Hospitalizations and urgent care visits related to drug-induced hyper- or hypoglycemia increase health care costs.[19,20]

Prevention

Potential strategies for preventing drug-induced changes in glycemia are listed in Table 8. Avoiding suspect drugs in high-risk patients is the best preventive method but is not always possible. The relative risks and benefits of drug administration must be weighed. For example, the benefits of using a protease inhibitor to treat HIV infection or an atypical antipsychotic to treat schizophrenia clearly outweigh the potential risk of hyperglycemia, even in a patient already with preexisting diabetes mellitus. Patients for whom drugs are prescribed that may alter glucose or insulin regulation require close monitoring for signs and symptoms of blood glucose dysregulation. Health care providers should also ask patients regarding the use of herbal supplements as some agents have been linked to changes in glycemic control (see Tables 1 and 2). Blood glucose should be obtained prior to initiating suspected drugs and periodically thereafter depending on assessment of the patient's risk. Close monitoring of blood glucose and of symptoms of hyper- and hypoglycemia is also needed after a patient has discontinued a drug that may induce glucose and/or insulin dysregulation.

Management

Discontinuation of the suspect drug is the best option to potentially reverse the drug-induced reaction but may not always be possible. This is especially true with drugs for which the benefits of continued use greatly outweigh the potential risks, such as protease inhibitors, atypical antipsychotics, or tacrolimus. For those agents that exhibit a dose-dependent effect on glucose levels (e.g., corticosteroids), reducing the dose may lessen or reverse the adverse drug reaction. Switching within the same pharmacological class to an agent that is not associated with hyper- or

Table 8. Strategies to Prevent Drug-induced Glucose and Insulin Dysregulation

- Obtain baseline fasting plasma glucose (FPG) prior to initiation of therapy with drugs known to affect glucose and/or insulin regulation particularly in patients with risk factors for type 2 diabetes mellitus or hypoglycemia.
- Monitor FPG within 4 weeks after initiating therapy and regularly thereafter (approximately every 3 to 6 months) during treatment with high-risk drugs.* Monitor more frequently in patients with preexisting disorder of glucose metabolism or if weight gain occurs.
- Monitor weight at each office visit.
- Inquire about symptoms of hyperglycemia and hypoglycemia at each office visit.
- Avoid or minimize administration of more than one drug that can induce glucose and/or insulin dysregulation.
- Avoid or minimize administration of drugs that may have pharmacokinetic or pharmacodynamic drug interactions with suspected drug.
- Use lowest dose for the shortest duration of administration if possible.

* Monitor FPG at baseline, at 12 weeks, and annually for patients taking atypical antipsychotics.[181]

Table 9. Management of Drug-induced Glucose and Insulin Dysregulation

Hyperglycemia and diabetes mellitus

- Discontinue or reduce dose of suspect drug if possible.
- Use suspect drug for shortest duration possible.
- Administer oral antidiabetic medications and/or insulin if patient develops diabetes mellitus.
- Implement appropriate dietary and lifestyle changes.
- Encourage exercise if weight gain is a contributing factor to development of hyperglycemia and diabetes mellitus.

Hypoglycemia

- Discontinue or reduce dose of suspected drug if possible.
- Use suspected drug for shortest duration possible.
- Implement dietary changes (e.g., frequent, small meals)

hypoglycemia should also be considered. For example, Spivak et al. reported on a case of olanzapine-induced diabetes mellitus that resolved following a switch to ziprasidone and resulted in the discontinuation of metformin treatment.[21] Short-term improvements in insulin resistance have been reported when a non-nucleoside reverse transcriptase inhibitor or abacavir was substituted for a protease inhibitor in HIV-1 infected patients.[22] Other management strategies are listed in Table 9. Most cases of drug-induced hyperglycemia are reversible once the offending drug is discontinued. An exception is when the drug causes permanent destruction of pancreatic beta cells (e.g., pentamidine). Once the offending drug is discontinued or the dose decreased, the time to improvement or return to baseline glycemia depends on the pharmacokinetic and/or pharmacodynamic properties of the drug. In most cases, the drug-induced hyperglycemia is reversible within days but may take longer for drugs that cause hyperglycemia via weight gain or peripheral insulin resistance such as atypical antipsychotics, protease inhibitors, or corticosteroids. Once a patient is diagnosed with diabetes mellitus, management of the hyperglycemia should follow current clinical practice guidelines. No approach or treatment strategy for the management of drug-induced hyperglycemia has been systematically studied to date. Patients with pre-existing diabetes may require an adjustment in their antidiabetic medications to compensate for the drug-induced changes in glycemic control. Initiation or discontinuation of antidiabetic agents may be required.

Information For Patients

Patients who receive prescribed medications that may induce diabetes should be educated about the symptoms of hyperglycemia and the importance of follow-up tests. Similarly, patients for whom medications that may induce hypoglycemia are prescribed should be educated about the symptoms of hypoglycemia and about the corrective actions that should be taken to elevate blood glucose. Patients who already have a diagnosis of diabetes should be informed that they may need to monitor their blood glucose concentrations more frequently and may need adjustments in their antidiabetic medication regimens. Patients should also be educated about the relative risks versus benefits of using the prescribed medication and to discontinue a suspected medication only with medical supervision. In addition, health care providers should inquire about the use of alternative medicine and herbal supplements and advise patients to use these only under medical supervision.

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Selected FDA Safety Alerts

Adderall XR (amphetamine)

FDA issued a Public Health Advisory to notify healthcare professionals that Health Canada, the Canadian drug regulatory agency, has suspended the sale of Adderall XR in the Canadian market. Adderall XR is a controlled release amphetamine used to treat patients with attention deficit hyperactivity disorder (ADHD). The Canadian action was based on U.S. post-marketing reports of sudden deaths in pediatric patients. FDA is continuing to evaluate these and other post-marketing reports of serious adverse events in children, adolescents, and adults being treated with Adderall and related products. Adderall XR is approved in the United States for the treatment of adults and pediatric patients 6 to 12 years old with ADHD, and Adderall, the immediate release formulation of the drug, is approved for pediatric patients with ADHD.

Agrylin (anagrelide hydrochloride)

Shire and FDA notified healthcare professionals about changes to the CONTRAINDICATIONS and WARNINGS sections of the prescribing information for Agrylin (anagrelide hydrochloride), a medication approved for the treatment of thrombocythemia secondary to myeloproliferative disorders to reduce platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events. Pharmacokinetic studies have revealed an eightfold increase in total exposure (AUC) to anagrelide hydrochloride in patients with moderate hepatic impairment. Use of anagrelide hydrochloride has not been studied in patients with severe hepatic impairment. Labeling changes include the contraindication to the use of Agrylin in patients with severe hepatic impairment. The WARNINGS section describes the need for dosage reduction in patients with moderate hepatic impairment and the necessity of monitoring these patients carefully for cardiovascular effects.

Aranesp (darbepoetin alfa)

FDA and Amgen notified healthcare professionals of revisions to the WARNINGS and PRECAUTIONS sections of the prescribing information for Aranesp, indicated for the treatment of chemotherapy-induced anemia in patients with nonmyeloid malignancies. This safety information alerts physicians to the adverse effects observed with other products in this class in association with off-label dosing strategies. Two recent investigational studies with other erythropoietic products permitted or required dosing to achieve hemoglobin levels of greater than 12 grams per deciliter. An increased frequency of adverse patient outcomes, including increased mortality and thrombotic vascular events were reported in these studies. As indicated in the Aranesp prescribing information, the target hemoglobin level should not exceed 12 grams per deciliter in men or women.

Avandamet (rosiglitazone maleate + metformin hydrochloride)

FDA and the Department of Justice have seized the remaining stocks of Paxil CR and Avandamet tablets manufactured by GlaxoSmithKline, Inc. Manufacturing practices for the two drugs, approved to treat depression and panic disorder (Paxil CR) and Type II Diabetes (Avandamet), failed to meet the standards laid out by FDA that ensure product safety, strength, quality and purity. FDA is not aware of any harm to consumers by the products subject to this seizure and it does not believe that these products pose a significant health hazard to consumers. Consequently, FDA urges patients who use these two drugs to continue taking their tablets and to talk with their health care provider about possible alternative products for use until the manufacturing problems have been corrected. FDA has determined that there are other products to treat the diseases for which these two products are used.

Avastin (bevacizumab)

FDA and Genentech notified healthcare professionals of revisions to the WARNINGS, PRECAUTIONS, ADVERSE EVENTS, and DOSAGE AND ADMINISTRATION sections of the Avastin labeling. Avastin, used in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. Arterial thromboembolic events, including cerebral infarction, transient ischemic attacks (TIAs), myocardial infarction (MI), and angina, occurred at a higher incidence in patients receiving Avastin in combination with chemotherapy as compared to those receiving chemotherapy alone. These events were fatal in some instances.

In randomized, active-controlled studies, the overall incidence of arterial thromboembolic events was increased with the use of Avastin in combination with chemotherapy (4.4 vs. 1.9 percent). The incidences of both cerebrovascular arterial events (1.9 vs. 0.5 percent) and cardiovascular arterial events (2.1 vs. 1.0 percent) were increased in patients receiving Avastin in combination with chemotherapy. In addition, there was a correlation between age (65 years and over) and the increase in risk of thromboembolic events. The risk of these events should be viewed in the context of Avastin's ability to improve overall survival in patients with metastatic colorectal cancer.

Crestor (rosuvastatin calicum)

FDA issued a public health advisory describing revisions to the WARNINGS, DOSAGE AND ADMINISTRATION, CLINICAL PHARMACOLOGY, and PRECAUTIONS sections of the labeling. The revisions include results from a Phase 4 pharmacokinetic study in Asian Americans and highlight important information on the safe use of Crestor to reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis), especially at the highest approved dose of 40 mg. At this time, the FDA is also making statements about the muscle and kidney safety of Crestor based on extensive review of available information.

Elidel (pimecrolimus)
Protopic (tacrolimus)

The FDA issued a public health advisory to inform healthcare providers and patients about a potential cancer risk from use of Elidel (pimecrolimus) and Protopic (tacrolimus), products that are applied to the skin. This concern is based on information from animal studies, case reports in a small number of patients, and how these drugs work. It may take human studies of ten years or longer to determine if use of Elidel or Protopic is linked to cancer. In the meantime, this risk is uncertain and FDA advises that Elidel and Protopic should be used only as labeled, for patients who have failed treatment with other therapies.

Invirase (saquinavir mesylate capsules and tablets)
Fortovase (saquinavir soft gelatin capsules)

Roche and FDA notified healthcare professionals about an Important drug interaction warning. Drug-induced hepatitis with marked transaminase elevations has been observed in healthy volunteers receiving rifampin 600 mg once daily in combination with ritonavir 100 mg/saquinavir 1000 mg twice daily (ritonavir boosted saquinavir). Roche now advises prescribers that Rifampin should not be administered to patients also receiving saquinavir/ritonavir (ritonavir boosted saquinavir) as part of combination antiretroviral therapy (ART) for HIV infection.

Phenergan (promethazine hydrochloride)

FDA and Wyeth notified healthcare professionals of revisions to the CONTRAINDICATIONS, WARNINGS/Use in Pediatric Patients, and DOSAGE AND ADMINISTRATION sections of the prescribing information for Phenergan. Phenergan is contraindicated for use in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Postmarketing cases of respiratory depression including fatalities, have been reported with use of Phenergan in pediatric patients less than two years of age. Caution should also be exercised when administering Phenergan to pediatric patients two years of age and older.

Xigris [drotrecogin alfa (activated)]

Eli Lilly and FDA notified healthcare professionals about revisions to the WARNINGS section of labeling for Xigris [drotrecogin alfa (activated)], a biological therapeutic product indicated for the treatment of adult patients with severe sepsis who are at high risk of death. This warning is based upon analyses of two clinical trial databases. Among patients with single organ dysfunction and recent surgery, all-cause mortality was numerically higher in the Xigris group compared to the placebo group. Patients with single organ dysfunction and recent surgery may not be at high risk of death and therefore may not be among the indicated population. Xigris should be used in these patients only after careful consideration of the risks and benefits.

ZyPREXA (olanzapine)

Eli Lilly and FDA notified healthcare professionals reports of medication dispensing or prescribing errors between the atypical antipsychotic ZyPREXA (olanzapine), indicated for the short-term and maintenance treatment of schizophrenia and for the short-term treatment of acute mixed or manic episodes associated with Bipolar I Disorder, and the antihistamine ZYRTEC (cetirizine HCI) marketed by Pfizer, indicated for the treatment of allergic rhinitis or chronic urticaria. These reports include instances where Zyprexa was incorrectly dispensed for Zyrtec and vice versa, leading to unnecessary adverse events or potential relapse in patients suffering from schizophrenia or bipolar disorder.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Enbrel (etanercept) injection, 50 mg/mL syringe
- Rocephin (Cetriaxone) 500 mg injection

Deletions

- Livostin (levocabastine) ophthalmic suspension
- Codeine phosphate oral solution
- Gyne-Lotrimin (clotrimazole) vaginal tablets
- Vasocon-A (naphazoline + antazoline) ophthalmic

Note: **Detailed information on these and other FDA safety alerts is available via the FDA homepage (*www.fda.gov*).**

FDA Safety Alerts

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.
- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.

Drug Information Service

- Patient-specific pharmacotherapy evaluation and management
- Comprehensive information about medications, biologics, and nutrients
- Critical evaluation of drug therapy literature
- Assistance with study design and protocol development
- Clinical trial drug safety monitoring
- Investigational drug information
- Parenteral nutrition assessment and management

301-496-2407
Pager 301-285-4661
Building 10, Room 1S-259